



Natural history, with clinical, biochemical, and molecular characterization of classical homocystinuria in the Qatari population

Al-Dewik, Nader ; Ali, Alaa ; Mahmoud, Yassmin ; Shahbeck, Noora ; Ali, Rehab ; Mahmoud, Laila ; Al-Mureikhi, Mariam ; Al-Mesaifri, Fatma ; Musa, Sara ; El-Akouri, Karen ; Almulla, Mariam ; Al Saadi, Reem ; Nasrallah, Gheyath K ; Samara, Muthanna ; Abdoh, Ghassan ; Rifai, Hilal Al ; Häberle, Johannes ; Thöny, Beat ; Kruger, Warren ; Blom, Henk J ; Ben-Omran, Tawfeg

Abstract: Classical homocystinuria (HCU) is the most common inborn error of metabolism in Qatar, with an incidence of 1:1800, and is caused by the Qatari founder p.R336C mutation in the CBS gene. This study describes the natural history and clinical manifestations of HCU in the Qatari population. A single center study was performed between 2016 and 2017 in 126 Qatari patients, from 82 families. Detailed clinical and biochemical data were collected, and Stanford-Binet intelligence, quality of life and adherence to treatment assessments were conducted prospectively. Patients were assigned to one of three groups, according to the mode of diagnosis: (a) late diagnosis group (LDG), (b) family screening group (FSG), and (c) newborn screening group (NSG). Of the 126 patients, 69 (55%) were in the LDG, 44 (35%) in the NSG, and 13 (10%) in the FSG. The leading factors for diagnosis in the LDG were ocular manifestations (49%), neurological manifestations (45%), thromboembolic events (4%), and hyperactivity and behavioral changes (1%). Both FSG and NSG groups were asymptomatic at time of diagnosis. NSG had significantly higher intelligence quotient, quality of life, and adherence values compared with the LDG. The LDG and FSG had significantly higher methionine levels than the NSG. The LDG also had significantly higher total homocysteine levels than the NSG and FSG. Regression analysis confirmed these results even when adjusting for age at diagnosis, current age, or adherence. These findings increase the understanding of the natural history of HCU and highlight the importance of early diagnosis and treatment. **SYNOPSIS:** A study in 126 Qatari patients with HCU, including biochemical, clinical, and other key assessments, reveals that patients with a late clinical diagnosis have a poorer outcome, hereby highlighting the importance of early diagnosis and treatment.

DOI: <https://doi.org/10.1002/jimd.12099>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-182917>

Journal Article

Published Version




The following work is licensed under a Creative Commons: Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.

Originally published at:

Al-Dewik, Nader; Ali, Alaa; Mahmoud, Yassmin; Shahbeck, Noora; Ali, Rehab; Mahmoud, Laila; Al-Mureikhi, Mariam; Al-Mesaifri, Fatma; Musa, Sara; El-Akouri, Karen; Almulla, Mariam; Al Saadi, Reem; Nasrallah, Gheyath K; Samara, Muthanna; Abdoh, Ghassan; Rifai, Hilal Al; Häberle, Johannes; Thöny, Beat; Kruger, Warren; Blom, Henk J; Ben-Omran, Tawfeg (2019). Natural history, with clinical, biochemical, and molecular characterization of classical homocystinuria in the Qatari population. *Journal of Inherited Metabolic Disease*, 42(5):818-830.
DOI: <https://doi.org/10.1002/jimd.12099>

ORIGINAL ARTICLE

Natural history, with clinical, biochemical, and molecular characterization of classical homocystinuria in the Qatari population

Nader Al-Dewik^{1,2}  | Alaa Ali¹ | Yassmin Mahmoud³ | Noora Shahbeck¹ | Rehab Ali¹ | Laila Mahmoud¹ | Mariam Al-Mureikhi¹ | Fatma Al-Mesaifri¹ | Sara Musa¹ | Karen El-Akouri¹ | Mariam Almulla¹ | Reem Al Saadi⁴ | Gheyath K. Nasrallah⁵ | Muthanna Samara⁶ | Ghassan Abdoh⁷ | Hilal Al Rifai⁷ | Johannes Häberle⁸ | Beat Thöny⁸ | Warren Kruger⁹ | Henk J. Blom¹⁰ | Tawfeg Ben-Omran^{1,11,12}

¹Clinical and Metabolic Genetics, Department of Pediatrics, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar

²College of Health and Life Sciences, Hamad Bin Khalifa University (HBKU), Doha, Qatar

³Children Rehabilitation Out Patient Clinics, Rumailah Hospital, Hamad Medical Corporation, Doha, Qatar

⁴Department of Dietetics and Nutrition, Hamad Medical Corporation, Doha, Qatar

⁵Department of Biomedical Sciences, Biomedical Research Center, College of Health Sciences, QU health, Qatar University, Doha, Qatar

⁶Department of Psychology, Kingston University London, London, UK

⁷Department of Pediatrics and Neonatology, Newborn Screening Unit, Hamad Medical Corporation, Doha, Qatar

⁸Division of Metabolism, University Children's Hospital and Children's Research Center, Zurich, Switzerland

⁹Cancer Biology Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania

Abstract

Classical homocystinuria (HCU) is the most common inborn error of metabolism in Qatar, with an incidence of 1:1800, and is caused by the Qatari founder p. R336C mutation in the *CBS* gene. This study describes the natural history and clinical manifestations of HCU in the Qatari population. A single center study was performed between 2016 and 2017 in 126 Qatari patients, from 82 families. Detailed clinical and biochemical data were collected, and Stanford-Binet intelligence, quality of life and adherence to treatment assessments were conducted prospectively. Patients were assigned to one of three groups, according to the mode of diagnosis: (a) late diagnosis group (LDG), (b) family screening group (FSG), and (c) newborn screening group (NSG). Of the 126 patients, 69 (55%) were in the LDG, 44 (35%) in the NSG, and 13 (10%) in the FSG. The leading factors for diagnosis in the LDG were ocular manifestations (49%), neurological manifestations (45%), thromboembolic events (4%), and hyperactivity and behavioral changes (1%). Both FSG and NSG groups were asymptomatic at time of diagnosis.

NSG had significantly higher intelligence quotient, quality of life, and adherence values compared with the LDG. The LDG and FSG had significantly higher methionine levels than the NSG. The LDG also had significantly higher total homocysteine levels than the NSG and FSG. Regression analysis confirmed these results even when adjusting for age at diagnosis, current age, or adherence. These findings

Abbreviations: 9-MMAS, 9-item Morisky Medication Adherence Scale; ADHD, attention deficit hyperactivity disorder; C, cytosine; CBS, cystathionine beta-synthase; C or Cys, cysteine; EL, ectopic lentis; FSG, family screening group; HCU, classical homocystinuria; ID, intellectual disability; IQ, intelligence quotient; LDG, late diagnosis group; Met,

methionine; NBS, newborn screening; NSG, newborn screening group; OMIM, Online Mendelian Inheritance in Man; P, protein; PCR, polymerase chain reaction; QoL, quality of life; R or Arg, arginine; T, thymine; tHcy, total homocysteine.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2019 The Authors. *Journal of Inherited Metabolic Disease* published by John Wiley & Sons Ltd on behalf of SSIEM

¹⁰Laboratory of Clinical Biochemistry and Metabolism, Department of General Pediatrics, Adolescent Medicine and Neonatology, University Medical Centre Freiburg, Freiburg, Germany

¹¹Department of pediatric, Weill Cornell Medical College, Doha, Qatar

¹²Division of Genetic & Genomics Medicine, Sidra Medicine, Doha, Qatar

Correspondence

Tawfeg Ben-Omran, Clinical and Metabolic Genetics, Department of Pediatrics, Hamad General Hospital, Hamad Medical Corporation, Doha, Qatar.
Email: tawben11@hotmail.com

Communicating Editor: Brian Fowler

Funding information

Qatar National Research Fund, Grant/Award Number: 7-355-3-088

increase the understanding of the natural history of HCU and highlight the importance of early diagnosis and treatment.

Synopsis: A study in 126 Qatari patients with HCU, including biochemical, clinical, and other key assessments, reveals that patients with a late clinical diagnosis have a poorer outcome, hereby highlighting the importance of early diagnosis and treatment.

KEYWORDS

classical homocystinuria, consanguinity, founder mutation p.R336C CBS gene, natural history, Qatar

1 | INTRODUCTION

Classical homocystinuria (HCU; OMIM 236200) is an autosomal recessive inborn error of methionine (Met) metabolism caused by deficiencies in the cystathionine beta-synthase (CBS) enzyme, with a worldwide incidence of approximately 1:200000 births.^{1,2} Although very rare elsewhere, HCU is the most common metabolic disease in Qatar, with an estimated incidence of 1:1800, the highest in the world, making it the most prevalent inherited monogenic disease in that nation.^{3,4} This high frequency is primarily attributed to a single founder Qatari mutation, p.R336C (c.1006C>T) (GenBank reference sequence NM_000071.2) in the *CBS* gene, a missense mutation replacing arginine (R or Arg) with cysteine (C or Cys), causing a severe vitamin B6 nonresponsive phenotype.^{4,5}

Clinically, untreated HCU patients exhibit multisystem manifestations, such as ectopia lentis (dislocation of the lens), nearsightedness, learning and intellectual disabilities (IDs), developmental problems, osteoporosis, and skeletal deformities. The latter include chest deformities, Marfanoid habitus, and scoliosis. Most important, HCU patients exhibit psychomotor retardation and life-threatening complications of the vascular system. They are characterized biochemically by high levels of plasma methionine (Met), as well as plasma and urine total homocysteine (tHcy).^{1,6-8}

In Qatar, with the advent of a national biochemical and molecular newborn screening (NBS) program in 2006, early detection and treatment of HCU, through administration of Met-restricted diets and betaine, has changed the natural history of the disease.^{4,9,10}

However, the current treatment options, based on a life-long Met- and protein-restricted diet supplemented with essential amino acids, are limited and difficult to maintain, especially during puberty, adolescence, and adulthood.¹¹ This study was conducted to delineate the clinical phenotypes, as well as their progressions and correlations with stage of diagnosis, in the homogenous Qatari population of vitamin B6 nonresponsive HCU caused by a single founder Qatari mutation (p.R336C).

2 | METHODS

A single center study (Clinical and Metabolic Genetic Division, Pediatrics Department, Hamad Medical Corporation, Doha, Qatar) was performed between 2016 and 2017 in patients with HCU. Detailed clinical and biochemical data were retrospectively collected. Stanford-Binet intelligence, quality of life (PedsQL) and adherence to treatment (Morisky scale) assessments were performed prospectively.

A questionnaire survey was developed at Hamad Medical Corporation and approved by Medical Research Center (see Ethics section). The questionnaire survey was filled out by the clinicians and consisted of four parts:

•**Part one.** The detailed natural history of HCU due to CBS deficiency in Qatari patients was documented and phenotypic diversity in both late and early diagnosed individuals was delineated. Information collected for each subject included: demographic data, assessment of anthropometric measurements (especially arm span-to-height and upper-to-lower segment ratios), detailed medical history (including a

three generation family history, course of the disease and any short- and long-term complications), as well as biochemical and radiological data. The natural history data were collected from patient files and, for any information not available in these files, from interviews of adult cases or parents of pediatric patients, as appropriate.

•*Part two.* Cognitive function was assessed in the enrolled patients using the Stanford-Binet Intelligence Scale (Versions 4 and 5), adopted from Child Development Center at Rumailah Hospital, administered only to those patients aged ≥ 3 years. The Stanford-Binet test is a cognitive ability assessment for measuring intelligence quotient (IQ). It assesses five domains of cognitive ability: fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory. Each of these factors is tested in two separate domains, verbal and nonverbal, yielding an IQ score.

•*Part three.* A measure of patient well-being was obtained with a quality of life (QoL) assessment, using the English and Arabic versions of PedsQL 4.0, administered only to patients ≥ 2 years old. For pediatric patients (aged ≤ 5 years), these were proxy reports and, for all others, they were self-reports. This method is considered effective and beneficial in Qatar for evaluating QoL in patients with HCU undergoing special dietary treatment and for determining psychosocial support needs for these patients and their families. The test uses four subjective QoL domains: emotional, physical, social, and cognitive function.

•*Part four.* Patient adherence/compliance to pharmacological and dietary management was assessed using the 9-item Morisky Medication Adherence Scale (9-MMAS). The pharmacological and dietary management parts of the questionnaire consisted of two sections: (a) administration of an assessment adapted from the well-validated Morisky-Green test and the 8-item MMAS. This adaptation was described previously.^{12,13} The resulting 9-MMAS included nine items measuring the presence or absence of nonadherent behaviors. In our study, good adherence was defined by a Morisky score of 11 or higher (ie, $\geq 85\%$). This cutoff was selected based on previous reports.^{14,15} (b) Patients were asked predefined follow-up questions to identify potential factors known to influence adherence to diet and treatment. These questions were related to patient lifestyle, income, and other treatment-related factors (eg, degree of social support, knowledge about treatment, and accessibility of the treating clinic). All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

3 | BIOCHEMICAL ANALYSIS

NBS for HCU is based on measuring tHcy and Met from dried blood spots.^{9,11,16}

4 | MUTATION ANALYSIS

CBS gene genotyping was performed using real-time polymerase chain reaction or DNA sequencing, as part of the clinical practice.^{4,5}

5 | PATIENTS' CLASSIFICATION

Patients were assigned to one of three groups according to mode of diagnosis/screening time: (a) late diagnosis group (LDG): symptomatic patients born primarily before the availability of the national NBS program; (b) family screening group (FSG): asymptomatic patients diagnosed because of a positive family history; and (c) newborn screening group (NSG): asymptomatic patients diagnosed by NBS.

6 | STATISTICAL ANALYSES

Descriptive statistics in the form of median, mean, range, and frequency, with percentages, were calculated.

Kaplan-Meier curves were constructed to assess differences in medians, among the three groups, of ocular manifestations and of survival. A log rank (Mantel Cox) test was used to assess this difference, with a two-tailed P -value $< .05$ regarded as statistically significant.

One-way analysis of variance (ANOVA) and the Bonferroni post-hoc test were conducted to assess differences among the three predictor groups (screening groups: NSG, FSG, and LDG) in relation to the different outcomes (IQ, QoL, Met tHcy, and adherence), with a P -value (two-tailed) $< .05$ considered to be statistically significant.

Pearson correlation analysis was performed among all variables to measure the strengths of their relationships. In addition, a partial correlation analysis was performed, adjusting first for current age only and then for age at diagnosis only. Strengths of these correlations (r) are reported along with the P -values.

Multiple linear regression analyses were conducted to test whether screening time (NSG, FSG, and LDG) (independent variable: IV) would predict psychological and medical factors, that is, IQ, QoL, Met, tHcy, and adherence (dependent variable: DV), before and after adjusting for current age and/or age at diagnosis (using separate regression models: with current age only, age at diagnosis only, and both current age and age at diagnosis). Linear regression models were also performed for screening time as IV, while adjusting for adherence, to predict different DVs. The

B value, which represents the strength and direction of the prediction along with the *P*-value and adjusted R^2 (indicating how much is explained by each prediction model) are reported for each regression analysis.

Multinomial logistic regression was used to test the strength of prediction for screening time (IV) (employing a reference group for comparisons among the three groups) in relation to the categorical variable adherence (differences for two categories). This was done before and after adjusting for confounder variables (current age or/and age at diagnosis).

All *P*-values presented are two-tailed, and *P*-values <.05 were considered to be statistically significant.

All statistical analyses were performed using the statistical package SPSS 24.0 (SPSS Inc., Chicago, Illinois).

7 | RESULTS

7.1 | Patient demographic data

The total sample included 131 patients, out of which, five patients were excluded from the study (three with different

mutations, one with Down syndrome, and one who did not follow up after the first visit).

Thus, the final sample included 126 patients with HCU (54 female, 72 male, current age: 1 to 41 years, mean: 17.41 years, SD: 10.24), from 82 families. HCU diagnosis was confirmed by elevated plasma tHcy and Met levels and the presence of homozygous p.R336C founder mutation (age at diagnosis: 2 weeks-20 years, mean: 4.30 years, SD: 4.46).

Of the 126 patients enrolled, 69 (55%) were in the LDG (age at diagnosis: mean: 7.5 years), 13 (10%) in the FSG (age at diagnosis: mean: 2 years), and 44 (35%) in the NSG (age at diagnosis: mean: 2 weeks) (see the next section, “Main and associated clinical manifestations,” for more details). All subjects in the study were followed regularly for at least 24 months. At enrollment, patients ranged in age from 5 to 41 years (mean: 24.54, SD: 7.19) in the LDG, from 13 to 30 years (mean: 16.88, SD: 4.77) in the FSG, and from 1 to 13 years (mean: 6.39, SD: 3.2) in the NSG (Table 1).

TABLE 1 Summary information for the three patient groups

	Late diagnosis group	Family screening group	Newborn screening group
N: 126 ^a	69	13	44
Age at diagnosis (median, range)	7 years (1 to 20 years)	1 year (1 month to 5 years)	2 weeks (2 weeks to 1 month)
Age at recruitment into study (median, range)	24 years (5 to 41 years)	14.5 years (13 to 30 years)	6.2 years (1 to 13 years)
Conditions at diagnosis			
Ocular	49%	N/A	N/A
Intellectual disability	42%	N/A	N/A
Thromboembolic	4%	N/A	N/A
Behavior	1%	N/A	N/A
Seizures	3%	N/A	N/A
Bone	N/A	N/A	N/A
Clinical symptoms during course of disease			
Ocular	92%	30%	N/A
Intellectual disability	79%	N/A	N/A
Cardiovascular abnormalities	29%	7.6%	N/A
Psychiatric	22%	7.6%	22.7%
Marfanoid habitus	98.5%	49%	7%
Scoliosis	51%	15%	N/A
Adherence to diet	15.6%	38.5%	61.4%
Total homocysteine levels, $\mu\text{mol/L}$ (median, range)	108 (42-363)	77.61 (31-102)	52.23 (19-130)
Methionine levels, $\mu\text{mol/L}$ (median, range)	829 (231-1524)	875 (632-1044)	381(20-1029)
IQ (median, range)	79.00 (39-113)	97.00 (89-110)	98.50 (84-116)
Quality of life (median, range)	86.25 (13-95)	91.25 (65-98)	97.50 (88-100)

^aFive patients (4%) died (1 dying at 3 years of age in a car accident and the other 4 during adulthood from thromboembolic events). Data was available for all 126 enrolled patients.

TABLE 2 Clinical features leading to diagnosis of classical homocystinuria in the late diagnosis group

Clinical features	Primary cause of diagnosis (% of patients)	Contributory cause (% of patients)
Ocular manifestations	49	58
Neurological manifestations	45	82
Thromboembolic events	4	0
Psychiatric manifestations	2	0
Musculoskeletal manifestations	0	7
Fair hair and skin	0	14

Consanguinity was found in 124 (98.4%) patients, 74 (60%) were first cousins and the remaining were either second cousins or from the same tribe.

There were 118 (94%) Qatari patients, with the remaining 8 (6%) patients from the Gulf Cooperation Council. All patients belonged to the same tribe and had the same founder (p.R336C) mutation.

Regarding education level, approximately 50% of the LDG group were either illiterate or attended a special school for the blind due to the serious ocular abnormalities associated with HCU, while patients in the NSG and FSG attended a regular school.

8 | MAIN AND ASSOCIATED CLINICAL MANIFESTATIONS

Patients in the LDG. The major factors leading to diagnosis were ocular manifestations in 34 (49%), neurological manifestations in 31 (45%), thromboembolic events in 3 (4%), and psychiatric manifestations in 1 (2%) (Tables 2 and S1). The median age for ocular manifestations was 7.5 years and, of the 34 patients, 29 (85%) had ectopic lentis (EL), 1 (3%) myopia, 3 (9%) EL plus secondary glaucoma, and 1 (3%) EL plus cataract.

The median age for neurological manifestations was 6 years and, of the 31 patients, 29 (94%) had ID and 2 (6%) had seizures. Of those patients with ocular manifestations as the major factors leading to diagnosis, 28 (82%) also had

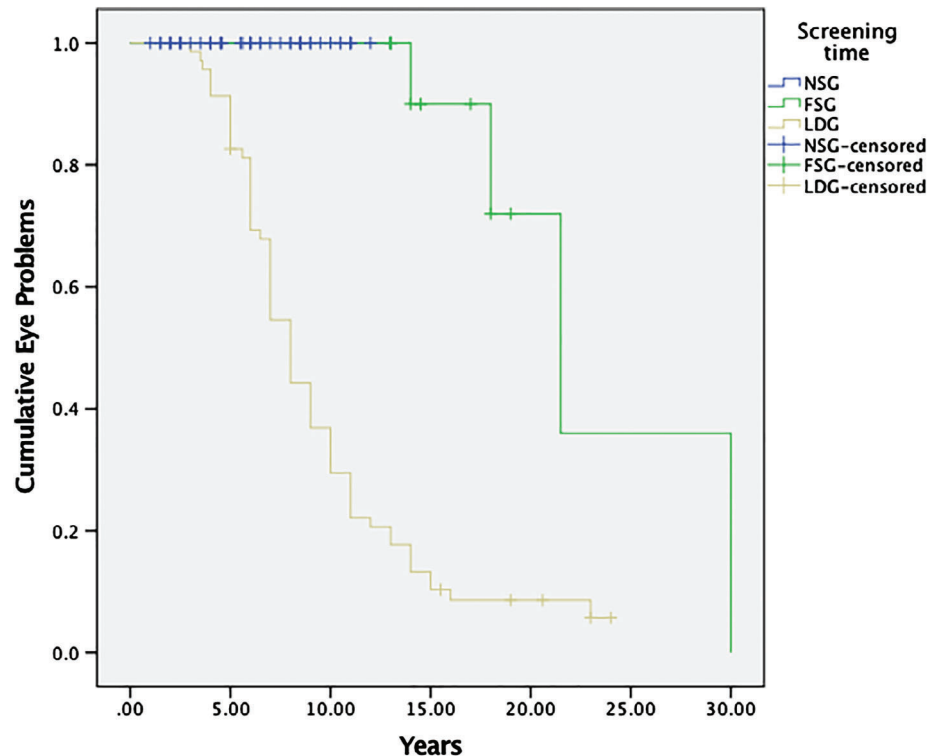
TABLE 3 Complications in the late diagnosis group during disease progression

Category	Complication	Number of patients	Onset at <18 years	Onset at ≥18 years
Skeletal	Marfanoid habitus	68	40	28
	Scoliosis	35	22	13
	Back pain, knee pain, neck pain or osteoporosis	38	17	21
	Fracture	20	16	4
	Other ^b	3	2	1
Central Nervous System (CNS)	Intellectual disability	49	49	None
	Learning disability	60	13	47
	Seizure	10	10	None
	White matter changes detected in head magnetic resonance imaging or computed tomography scan	13	7	6
	Other (extrapyramidal symptoms)	2	None	2
Cardiovascular	All	20	10	10
Psychiatric	Aggression or/and behavioral abnormalities	56	12	44
	Other psychiatric disorders	15	7	8
Ocular	Myopia	13	13	None
	Lens dislocation	61	54	1
	Eye surgery	41	35	6
	Other complications in ectopic lentis, for example, cataract and glaucoma	20	18	2
Rare ^a	All	32	20	12

^aRare hypertension (14%), fatty liver (7%), skin disorders (6%), bronchiectasis (4%), chronic pancreatitis (4%), and gastrointestinal bleeding (1%).

^bOther (degenerative lumbar disc disease with spondylolisthesis and pars defect at 38 years, two below 18 years presented with osteolytic lesion suggestive of nonossifying fibroma and other with cystic sclerotic lesions and periosteal reaction suspected Ewing's sarcoma).

FIGURE 1 Kaplan-Meier curves showing onset of ocular symptoms amongst NSG, FSG and LDG



associated neurological manifestations such as ID or seizures and 1 (3%) had musculoskeletal manifestations (Table 2).

Of those patients with neurological manifestations as the major factors leading to diagnosis, 18 (58%) also had associated ocular manifestation such as myopia and EL, and 3 (7%) had musculoskeletal abnormalities such as skeletal deformities (Table 2).

Other associated clinical manifestations at the time of diagnosis were fair hair and skin in 10 (14%) patients.

The following complications were observed in the LDG: 98.5% with Marfanoid habitus, 92% ocular abnormalities, 79% ID, 51% scoliosis, 29% fractures, 29% cardiovascular abnormalities, and 22% psychiatric illnesses. In addition, 6% developed severe thromboembolic events, leading to death in adulthood (Table 3).

Other complications included hypertension (14%), fatty liver (7%), skin disorders (6%), bronchiectasis (4%), chronic pancreatitis (4%), and gastrointestinal bleeding (1%) (Table 3).

Patients in the FSG. All patients in this group were asymptomatic at the time of diagnosis. However, during course of their disease, 49% developed mild Marfanoid habitus, 15% scoliosis, 30% ocular complications, 15% chronic pancreatitis, and 8% mitral valve prolapse (Table S2).

Patients in the NSG. The mean age of diagnosis and initiation of treatment was approximately 2 weeks. During the course of their disease, 22.7% of patients developed behavioral manifestations and 7% developed Marfanoid habitus

(Table 1). As previously reported, NBS was performed based on blood tHcy levels.⁹

Comparison of ocular manifestations among groups. Kaplan-Meier analyses (Figure 1) showed significant differences among groups in incidence of ocular symptoms during the course of disease, with such manifestations observed in 92% of the LDG, 30% of the FSG, and none of the NSG patients ($P \leq .001$).

A survival analysis was not feasible because of the relatively low mortality exhibited in the LDG group during the study, with 85% of patients still alive at age 31 years. No mortality associated with HCU was observed in the NSG or FSG. Thus, without a longer duration follow-up, survival differences among the three groups could not be assessed.

9 | DIFFERENCES AMONG THE SCREENING TIME GROUPS IN PSYCHOLOGICAL FACTORS, ADHERENCE, AND BIOCHEMICAL PROFILES

IQ. The IQ test was administered to 89 (70%) of the patients. Of those not tested for IQ, 21 (17%) refused, 11 (10%) were < 3 years old, and 5 (4%) had died earlier in the study. The IQ test was, therefore, administered to 52 patients from the LDG, 9 from the FSG, and 28 from the NSG (Table 4).

TABLE 4 IQ, QoL, adherence, Met level, and total homocysteine level values in different screening time groups and in all patients

Outcomes	Groups	No	Mean	SD	SE	95% confidence interval for mean		Range	
						Minimum	Maximum	Minimum	Maximum
IQ	NSG	28	99.89	8.689	1.642	96.52	103.26	84	116
	FSG	9	98.11	8.313	2.771	91.72	104.50	89	110
	LDG	52	80.31	12.420	1.722	76.85	83.77	39	113
	Total	89	88.27	14.464	1.533	85.22	91.32		
QoL	NSG	34	96.52	3.626	0.622	95.26	97.79	88	100
	FSG	13	89.81	8.424	2.336	84.72	94.90	65	98
	LDG	60	82.62	13.589	1.754	79.11	86.13	13	95
	Total	107	87.91	12.450	1.204	85.52	90.30		
Adherence	NSG	44	10.4318	2.32677	0.35077	9.7244	11.1392	5.00	13.00
	FSG	13	9.0000	2.91548	0.80861	7.2382	10.7618	2.00	12.00
	LDG	64	7.1406	3.04916	0.38114	6.3790	7.9023	2.00	13.00
	Total	121	8.5372	3.17028	0.28821	7.9666	9.1078		
Met	NSG	44	388.17	277.006	41.760	303.95	472.39	20	1029
	FSG	13	852.45	138.323	38.364	768.86	936.03	632	1044
	LDG	67	815.93	283.748	34.665	746.71	885.14	231	1524
	Total	124	667.97	339.736	30.509	607.58	728.36		
Total homocysteine	NSG	44	61.19	28.306	4.267	52.58	69.79	19	130
	FSG	13	73.51	23.359	6.479	59.39	87.63	31	102
	LDG	67	119.76	60.493	7.390	105.01	134.52	42	363
	Total	124	94.13	55.569	4.339	85.54	102.72		

Abbreviations: FSG, family screening group; IQ, intelligence quotient; LDG, XXX; met, methionine; NBS, newborn screening; QoL, quality of life.

Quality of life (QoL). The QoL test was administered to a total of 107 patients, from the LDG ($n = 60$), FSG ($n = 13$), and NSG ($n = 34$). Of the 19 individuals not tested, 9 were younger than 2 years old, 5 had died, and 4 (all from the LDG) refused to participate (Table 4).

Patients' adherence. Patients' adherence was assessed for 120, from the LDG ($n = 64$), FSG ($n = 13$), and NSG ($n = 44$). Adherence scores ranged from 3 to 13 (median 10) (Morisky scores: nonadherence: <11 ; adherence: ≥ 11) (Table 4).

Biochemical profiles, based on sulfur metabolite levels. Plasma metabolite levels were determined for 124 patients, including 67 subjects from the LDG, 13 from the FSG, and 44 from the NSG.

One-way ANOVA was conducted to compare the three screening time groups in relation to the different outcomes. The analysis indicated significant differences among the screening time groups (NSG, FSG, and LDG) for IQ ($F(2, 86) = 32.69$; $P \leq .001$; $\eta^2 = .432$), QoL ($F(2, 104) = 18.15$; $P \leq .001$; $\eta^2 = .259$), Met levels ($F(2, 121) = 36.63$;

$P \leq .001$; $\eta^2 = .377$), tHcy levels ($F(2, 121) = 20.84$; $P \leq .001$; $\eta^2 = .256$), and adherence to diet and medication ($F(2, 118) = 18.30$; $P \leq .001$; $\eta^2 = .237$).

Bonferroni post-hoc test results indicated that the NSG had significantly higher IQ, QoL, and adherence values compared with the LDG ($P \leq .001$). In addition, the FSG had significantly higher IQ values than the LDG ($P \leq .001$). The LDG and FSG had significantly higher Met levels than the NSG ($P \leq .001$). The LDG also had significantly higher tHcy levels than the NSG ($P \leq .001$) and FSG ($P = .006$).

We characterized adherence to diet and medications into two categories: adherent (cutoff ≥ 11) and non-adherent (<11). There was a significant relationship between adherence and screening time groups ($\chi^2(2, N = 121) = 24.16$, $P \leq .001$). Patients in the NSG were more likely to be in the adherent category ($N: 27/44 = 61.4\%$), compared with those in the FSG ($N: 5/13$; 38.5%) or LDG ($N: 10/64$; 15.6%). Cumulatively, therefore, the earlier the diagnosis, the more likely a patient would be adherent.

10 | CORRELATIONS BETWEEN SCREENING TIME AND THE MEDICAL AND PSYCHOLOGICAL FACTORS

Screening time with other factors. There was a significant negative correlation between screening time and IQ ($r = -.636$, $n = 89$, $P \leq .001$) (strong), QoL ($r = -.509$, $n = 107$, $P \leq .001$) (moderate), and adherence ($r = -.486$, $n = 121$, $P \leq .001$) (moderate). These results indicated that the earlier the screening time, the higher the IQ, QoL, and adherence. Screening time also had significant positive correlations with plasma levels of Met ($r = .571$, $n = 124$, $P \leq .001$) and tHcy ($r = .497$, $n = 124$, $P \leq .001$). Thus, the higher the screening time, the more abnormal biochemical profile. Adjusted for current age, the correlations between screening time and IQ ($r = -.268$, $P = .012$), adherence ($r = -.211$, $P = .022$), Met levels ($r = .299$, $P = .001$), and tHcy ($r = .300$, $P = .001$) became weaker but were still significant, while for QoL the correlation became nonsignificant.

When adjusted for age at diagnosis, correlations between screening time and adherence ($r = -.272$, $P = .003$), IQ ($r = -.381$, $P \leq .001$), QoL ($r = -.310$, $P \leq .001$), Met ($r = .505$, $P \leq .001$), and tHcy ($r = .296$, $P = .001$) also were weaker than for nonadjusted values, but still significant.

Adherence with other factors. There was a significant positive correlation between adherence and both IQ ($r = .302$, $n = 88$, $P = .004$) and QoL ($r = .252$, $n = 106$, $P = .009$). The higher the adherence, the higher the IQ and QoL. In contrast, adherence was negatively correlated with plasma levels of Met ($r = -.357$, $n = 121$, $P \leq .001$) and tHcy ($r = -.548$, $n = 121$, $P \leq .001$). Thus, with lower adherence, metabolic abnormalities were higher. Only the correlation between adherence and tHcy levels remained significant when data were adjusted for current age ($r = -.438$, $P \leq .001$) or age at diagnosis ($r = -.452$, $P \leq .001$). The correlation of adherence with Met levels ($r = -.246$, $P = .007$) remained significant also when data were adjusted for age at diagnosis.

QoL and IQ with other factors. There was a significant positive correlation between QoL and IQ ($r = .638$, $n = 88$, $P \leq .001$). There were significant negative correlations between QoL and Met levels ($r = -.195$, $n = 106$, $P = .045$), QoL and tHcy levels ($r = -.302$, $n = 106$, $P = .002$), IQ and Met levels ($r = -.340$, $n = 88$, $P = .001$) and IQ and tHcy levels ($r = -.376$, $n = 88$, $P \leq .001$). However, only the correlation between QoL and IQ remained significant when data were adjusted for current age ($r = .452$, $P \leq .001$) or age at diagnosis ($r = .533$, $P \leq .001$).

11 | SCREENING TIME PREDICTING PSYCHOLOGICAL AND MEDICAL FACTORS BEFORE AND AFTER ADJUSTING FOR CURRENT AGE AND/OR AGE AT DIAGNOSIS

Linear regression analyses were conducted to test whether screening time (in the NSG, FSG, and LDG) predicted psychological and medical factors, with or without adjusting data for current age or age at diagnosis.

Without age-related adjustments, the regression model was significant for QoL ($F(1, 105) = 36.63$, $R^2 = .259$; $P \leq .001$), IQ ($F(1, 87) = 58.97$, $R^2 = .404$; $P \leq .001$), adherence ($F(1, 119) = 36.82$, $R^2 = .236$; $P \leq .001$), plasma Met levels ($F(1, 122) = 58.99$, $R^2 = .326$; $P \leq .001$), and plasma tHcy levels ($F(1, 122) = 40.10$, $R^2 = .247$; $P \leq .001$).

Screening time predicted QoL ($B = -6.96$, $P \leq .001$), IQ ($B = -10.06$, $P \leq .001$), adherence ($B = -1.65$, $P \leq .001$), Met levels ($B = 208.22$, $P \leq .001$), and tHcy levels ($B = 29.67$, $P \leq .001$).

With data adjusted for age at diagnosis, the prediction model for screening time indicated significance for QoL ($B = -6.149$, $R^2 = .418$, $P = .001$), IQ ($B = -7.863$, $R^2 = .289$, $P \leq .001$), adherence ($B = -1.44$, $R^2 = .252$, $P = .001$), Met levels ($B = 275.44$, $R^2 = .348$, $P \leq .001$), and tHcy levels ($B = 25.69$, $R^2 = .250$, $P \leq .001$).

These results indicated that age at diagnosis did not explain the relationship between screening time and QoL, IQ, adherence, Met levels, or tHcy levels.

From the adjusted variable, the age at diagnosis was a significant predictor only for Met levels ($B = -17.96$, $P = .047$), when considering the screening time.

When data were adjusted for current age, the prediction model for screening time indicated significance for IQ ($B = -5.777$, $R^2 = .447$, $P = .007$), adherence ($B = -1.020$, $R^2 = .253$, $P = .030$), Met levels ($B = 163.69$, $R^2 = .333$, $P = .001$), and tHcy levels ($B = 28.56$, $R^2 = .248$, $P = .001$). In contrast, with this adjustment, there was no longer significance in the prediction model for QoL ($B = -2.832$, $R^2 = .315$, $P = .118$). Thus, current age explained the relationships between screening time and QoL, but not those between screening time and IQ, adherence, Met, or tHcy levels.

From the adjusted variable, current age was a significant predictor for IQ ($B = -0.505$, $P = .011$) and QoL ($B = -0.492$, $P = .004$), when considering the screening time.

With adjustments for both current age and age at diagnosis, the prediction model for screening time showed no significance for all DVs, except Met levels ($B = 219.19$, $R^2 = .368$, $P \leq .001$) and tHcy ($B = 26.02$, $R^2 = .250$,

$P = .005$). This indicated that current age and age at diagnosis explained the relationship between screening time and most of the DVs, except Met and tHcy levels. From the adjusted variable, current age was a significant predictor for IQ ($B = -0.470$, $P = .032$) and QoL ($B = -0.520$, $P = .005$) when considering screening time and age at diagnosis, while age at diagnosis was a significant predictor for Met levels ($B = -23.97$, $P = .012$) when considering screening time and current age.

We constructed a new model using screening time and adherence to predict IQ, QoL, Met levels, and tHcy levels. The prediction model for screening time indicated significance for QoL ($B = -6.369$, $R^2 = .271$, $P \leq .001$), IQ ($B = -9.659$, $R^2 = .402$, $P \leq .001$), Met ($B = 195$, $R^2 = .346$, $P \leq .001$), and tHcy levels ($B = 17.59$, $R^2 = .374$, $P \leq .001$). Adherence was also significantly related to tHcy levels ($B = -6.61$, $R^2 = .374$, $P \leq .001$), with adjustment for screening time. This indicated that adherence did not explain relationships with any DV.

We then employed multinomial logistic regression with adherence to diet and medications (adherent: cutoff point ≥ 11 and nonadherent: <11) as the DV and screening time as the IV. The prediction model indicated significance ($\chi^2(2, N = 121) = 24.74$, $P \leq .001$). Results indicated that patients in the NSG were more likely to be in the adherent category than were those in the LDG (odds ratio: 8.58, 95% confidence interval [CI]: 3.46–21.25), with no significant differences between NSG and FSG, or between FSG and LDG. With adjustments for current age and/or age at diagnosis, there was no longer a significant difference between the NSG and LDG, relative to adherence.

12 | DISCUSSION

This study supports a close association between age of diagnosis and the outcome of HCU severity. In particular, early detection by NBS (patients in the NSG), leading to early initiation of treatment, was associated with a markedly less severe disease course. In contrast, patients in the LDG, diagnosed between ages 1 and 20 years (median 7 years old), and recruited into the study at ages 5 to 41 years (median 24 years), presented with a variety of serious manifestations, primarily ocular or neurological, along with numerous associated symptoms including skeletal abnormalities. The constellation of symptoms experienced by these patients is what ultimately led to their diagnosis of HCU. The NSG patients, with all 44 patients in the study diagnosed at approximately 2 weeks of age, exhibited no primary or associated clinical presentations at diagnosis. Fourteen NSG patients developed symptoms, especially aggressiveness and hyperactive behaviors, as their disease progressed, but no ocular symptoms or ID occurred in this subcohort by the end of this study. These

patients were recruited into the study at ages ranging from 2 weeks to 13 years old (median, 6 years old) and were, therefore, younger than the other groups during the study.

The median age of the NSG cohort (6 years) is similar to the median age when LDG patients were first diagnosed (7 years). However, children in the NSG had far fewer complications upon diagnosis than did those in the LDG. Although about 22.7% (10) of NSG patients developed behavioral manifestations, during the time covered by this study they did not develop other disabilities, including ocular or IDs, the primary diagnoses of patients in the LDG.

Our results were consistent with those from a long-term retrospective study in Ireland of 25 patients under age 24 with HCU, bearing the Irish mutation p.I278T. That previous study suggested that lens dislocation could be prevented, or at least significantly delayed, in patients whose tHcy levels were consistently decreased from an early age. Early Hcy-lowering treatment was also associated with a reduced risk of overall ocular complications, including worsening myopia.¹⁷

More recent data from the Irish NBS program was used to compare the mental capabilities of 23 pyridoxine non-responsive individuals with HCU with those of 10 unaffected sibling controls.¹⁸ Of the 23 patients identified, 19 were diagnosed with HCU through NBS and treated early in life (within 6 weeks of birth), two cases were detected late (age 2 years), and two had been untreated at the time of assessment. Overall, 13 of the 19 patients in the early treated group (mean age 14 years; range 4 to 25) were compliant with treatment and had no complications, whereas the remaining 6 (mean age 20 years; range 14 to 26), who had poor compliance, developed complications. Mean full-scale IQ was normal in the compliant group but low in the poorly compliant and noncompliant groups.¹⁸ Despite the relatively small numbers, these results suggested that early treatment with good biochemical control prevented mental retardation and our study confirmed the findings from this Irish cohort.

The IQ results in our study illustrated that those in the LDG had more intellectual deficits than did those in the other two groups. The mean IQ score in the LDG was significantly lower than in the NSG or FSG. Similarly, in an earlier study utilizing healthy siblings as controls, showed that patients diagnosed by NBS had better developmental and cognitive outcomes than did those diagnosed later.¹⁹ These results remained significant in the correlation analysis even when we adjusted for current age and age at diagnosis.

Our study, unlike previous studies, included bigger sample size in each group and we were able to compare the results to the FSG. In addition, we also found that LDG has lower QoL compared to NSG. This is related to impairments in different domains including physical, emotional, social, and school. This indicates that early screening can detect

problems early on, and thus provide patients with suitable early treatment and interventions. These results remained significant when adjusting for age at diagnosis but disappeared when adjusting for current age. This means that patients' current age determined differences in QoL levels.

The benefits of Hcy-lowering therapy in individuals with psychiatric symptoms associated with HCU were first demonstrated in a study of 12 late-diagnosed patients.²⁰ Three of these patients were never treated effectively and had serious psychological disorders, with premature deaths. The remaining 8 patients ranged from 1 to 26 years of age (mean 13 years) had psychiatric symptoms, including irritability, attention deficit hyperactivity disorder, apathy, and psychosis. Treatment was associated with a striking improvement in behavior and intellectual development, correlating with biochemical normalization.

In our study NSG had lower biochemical levels (Hcy and Met levels) compared to the LDG and also lower levels of Met compared to FSG. These results are also reflected and strongly related to adherence to medical therapy and diet by our participants in this study. The results in relation to biochemical and adherence levels remained significant even when adjusting for current age or age at diagnosis. This means that early screening itself led to better adherence to therapy and diet regardless of the age of the patient and thus better biochemical levels.

Regarding compliance with medical therapy, the proportion of adherent to nonadherent patients was 1:6.4 in the LDG, 1:2.6 in the FSG, and 1.6:1 in the NSG. The age at which the patients were diagnosed was strongly correlated with compliance, with the group diagnosed latest (LDG) being the least compliant. However, it must be noted that most patients in the FSG, similar to those in the NSG, were diagnosed in infancy and, yet, those in the FSG were less compliant than those in the NSG. This is likely attributable to patients in the FSG being older, on average, during the study, and illustrates how difficult compliance can be to achieve once the individual has been exposed to normal protein foods, even in infancy, and how increasingly difficult it becomes for patients to remain adherent at ages beyond childhood.

In this study, we found significant positive correlations between adherence and both IQ and QoL, which disappeared when adjusting for age at diagnosis or current age. In contrast, adherence was negatively correlated with plasma levels of Met and tHcy even when adjusting for age at diagnosis. tHcy also remained significant when adjusting for current age.

Regression analysis supports this and gave a new insight into these relationships. High adherence was significantly related to lower tHcy levels, with adjustment for screening time.

Compliance with medical therapy was poorer in the LDG and the disease progressed markedly in these patients, with additional adverse manifestations developing in the years following their diagnosis. In contrast, patients in the FSG, identified based on family history of HCU, were diagnosed earlier than those in the LDG, at ≤ 5 years of age (median 2 years), and initially presented with no clinical manifestations. However, as their disease progressed, they developed many symptoms similar to those in the LDG. They were recruited into the study at 12 to 29 years old (median 13 years old). Only two patients in the FSG had not yet developed any HCU-related clinical manifestations by the time this study was performed, and these two children were among the youngest in this group. A combination of lack of adherence to treatment and thus cumulative effects of exposure to abnormally high tHcy and Met levels likely led to these poor outcomes. Of note, even patients with excellent adherence to treatment could not achieve normalization of tHcy levels. This was not related to age at diagnosis or/and current age.

Although a restricted diet decreases tHcy levels in fully compliant patients to varying degrees, many patients never achieve normalization.¹¹ Treatment must be continued throughout life, as periods of poor metabolic control have cumulative deleterious effects that can lead to severe complications and premature death. However, compliance with diet is often poor because of the complexities of the diets and their severe restrictions.²¹ Adherence generally deteriorates during adolescence and adulthood^{22,23} and can be particularly challenging for patients with a late diagnosis.²⁴ Overall, in our study, patients in the NSG were under better metabolic control than those in the other groups, consistent with their higher compliance. However, all groups had median tHcy levels substantially higher than normal values ($\leq 15 \mu\text{mol/L}$).¹⁷ Patients in the LDG and FSG groups also had higher Met levels than did those in the NSG.

The patients in NSG and FSG, although on average diagnosed only a few months apart, showed marked differences in adherence to treatment and in clinical manifestations. These treatments varied among patients, with most prescribed a low protein diet only while others receiving additional betaine supplementation. These differences in clinical manifestations were likely due to lower adherence to treatment and higher ages, as the mean age of patients in the FSG was older than that of patients in the NSG. This lower adherence was possibly compounded by the initial difficulty for patients of accepting the low protein diet after having been introduced to foods with standard protein contents. Age is a known risk factor for lack of compliance in adolescents,^{22,23} and years of exposure to abnormally high tHcy levels likely contributed to cumulative damage.

Consistent with the course of disease progression, plasma tHcy and Met levels indicated greater metabolic control in

the NSG than in the FSG and, even more so, than in the LDG. Some of these differences in disease severity might be related to the discrepancies in compliance with treatment observed among the three groups, leading to the higher tHcy levels. Adherence to treatment was inversely correlated with age of diagnosis, with the group diagnosed at birth achieving the highest compliance to treatment. In the NSG, FSG, and LDG, approximately 61%, 39%, and 15%, respectively, were identified as fully adherent to treatment. This was consistent with the general knowledge that dietary compliance becomes more challenging in adolescent and adult patients, as compared with in young children.^{22,23} Thus, the older ages of patients in the FSG at study enrollment may partially account for the poorer metabolic control, compared with those in the NSG. It was notable that, despite the high compliance in the NSG, plasma tHcy levels were still well above normal and, as the disease progressed, several clinical manifestations, especially aggressive or hyperactive behavior, were noted in a substantial percentage of patients aged 3 to 11 years. It should be noted that patients in the NSG ranged in age from 1 to 13 years, and it is conceivable that additional clinical manifestations of the disease may appear as this patient group ages further, including cumulative damage from elevated tHcy levels.

This study was conducted in Qatar, where the incidence of HCU is extremely high, attributed primarily to parental consanguinity and caused by a single founder mutation in the *CBS* gene, p.R336C.^{4,5} Indeed, about 99% of the patients enrolled in our study were from consanguineous families. It might be suggested that such unique aspects of this patient population would limit extrapolation of these findings to the broader worldwide population of HCU sufferers. Nonetheless, these patients, especially those in the LDG and FSG groups, exhibited an array of severe multisystem complications characteristic of HCU caused by other *CBS* mutations.² Furthermore, the importance of early diagnosis and the adverse impacts of inconsistent treatment compliance observed here were also supported by several other studies^{17,18} performed in various patient populations.

The regression analysis in this study confirms these results by giving predictions models and the strength for each. We found that late screening time predicts lower QoL, IQ, adherence, and higher Met levels and tHcy levels even when adjusting for age at diagnosis. When adjusting for current age, all results remained significant except for QoL. Thus, current age explained the relationships between screening time and QoL, but not those between screening time and other factors.

In addition, late screening time significantly predicted lower QoL and IQ, and higher Met and tHcy levels, even when taking into account adherence.

This indicates that early screening is essential in explaining psychological, cognitive, and biochemical outcomes regardless of age at diagnosis, current age, and/or adherence levels. Thus, additional factors can explain these relationships. We can only speculate that, for example, family awareness about the disease, early medical treatment or socioeconomic status including educational levels of the parents could explain these relationships. Further studies to investigate these factors are needed.

Our results contribute to an improved understanding of the natural history of HCU, supporting the effectiveness of early diagnosis, especially by NBS, and dietary and pharmacological treatment compliance, for improving clinical outcomes. With a mandatory and highly sensitive NBS in place, the number of patients diagnosed late or through family diagnosis should dwindle. As the NSG patients age, a future age-matched comparison to this historical LDG cohort will be possible.

In addition, these results suggest a need for new treatment strategies, potentially leading to improved metabolic control with a lessened requirement for diet compliance. Consistent with our observations, existing treatment regimens requiring life-long dietary restrictions make it challenging for patients to remain compliant, especially beyond the childhood years.²¹⁻²⁴ Thus, even with early diagnosis by NBS and relatively high compliance, patients in our study still developed some of the adverse clinical consequences of their disease. Long-term cumulative exposure to elevated tHcy levels may uncover additional sequelae not yet apparent in the pediatric NSG cohort, and it may therefore be too soon to ascertain whether long-term complications have been avoided in this group, despite their abnormally high tHcy levels.

ACKNOWLEDGMENT

This report was made possible by National Priorities Research Program grant no 7-355-3-088 from the Qatar National Research Fund (a member of Qatar Foundation). The statements made herein are solely the responsibility of the authors.

AUTHOR CONTRIBUTIONS

Design of the study: N.A.-D., A.A., G.N., J.H., W.K., H.J.B., B.T. and T.B.-O. Recruited patients into the study as well as provided clinical data: A.A., N.S., R.A., L.M., S.M., M.A.-M., F.A.-M., T.B.-O. Designed a questionnaire survey N.A.-D. and A.A. Performed IQ test and analysis: Y.M. Interviewed patients and collected survey questionnaires' results: A.A. Statistical analysis: M.S. and N.A.-D. Provided Biochemical results for HCU patients through

NBS program: G.A., H.A.R. Provided genetic counseling for patients and their families: K.E.-A., M.A. Provided medical formula such as low methionine diet, low protein and Betaine for patients: R.A. Wrote the manuscript: N.A.-D., A.A., M.S., and T.B.-O. In addition, all authors participate in analysis and interpretation of data and provided critical revisions to the various manuscript drafts. All authors read and approved the final manuscript.

ETHICS STATEMENT

This project was approved by the Hamad Medical Corporation Research Ethics Committee (reference number MRC 14221/14). Informed consent was obtained from all participants, or their legal guardians, included in the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Nader Al-Dewik  <https://orcid.org/0000-0001-5739-1135>

REFERENCES

- Mudd SH, Finkelstein JD, Irreverre F, Laster L. Homocystinuria: an enzymatic defect. *Science*. 1964;143(3613):1443-1445.
- Mudd SH, Skovby F, Levy HL, et al. The natural history of homocystinuria due to cystathionine beta-synthase deficiency. *Am J Hum Genet*. 1985;37(1):1-31.
- Al-Dewik N, Ali A, Shahbeck N, et al. Natural history, characterization and outcome of classical homocystinuria in the Qatari population. The 13th International Congress of Inborn Errors of Metabolism. R. Giugliani. Rio De Janeiro, Brazil. *The Journal of Inborn Errors of Metabolism and Screening*. 2017;4:138.
- Zschocke J, Kebbewar M, Gan-Schreier H, et al. Molecular neonatal screening for homocystinuria in the Qatari population. *Hum Mutat*. 2009a;30(6):1021-1022.
- El-Said MF, Badii R, Bessiso MS, et al. A common mutation in the CBS gene explains a high incidence of homocystinuria in the Qatari population. *Hum Mutat*. 2006a;27(7):719.
- Magner M, Krupkova L, Honzik T, Zeman J, Hyanek J, Kozich V. Vascular presentation of cystathionine beta-synthase deficiency in adulthood. *J Inherit Metab Dis*. 2011;34(1):33-37.
- Quintas S, Dotor-Garcia Soto J, Alonso-Cerezo MC, Carreras MT. Late diagnosis of homocystinuria in an adult after extensive cerebral venous thrombosis. *Pract Neurol*. 2018;18(1):49-51.
- Sacharow SJ, Picker JD, Levy HL. Homocystinuria Caused by Cystathionine Beta-Synthase Deficiency. 2004 Jan 15 [Updated 2017 May 18]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. *GeneReviews*[®] [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1524/>
- Gan-Schreier H, Kebbewar M, Fang-Hoffmann J, et al. Newborn population screening for classic homocystinuria by determination of total homocysteine from Guthrie cards. *J Pediatr*. 2010a;156(3):427-432.
- Woods E, Dawson C, Senthil L, Geberhiwot T. Cerebral venous thrombosis as the first presentation of classical homocystinuria in an adult patient. *BMJ Case Rep*. 2017;2017:bcr2016217477.
- Morris AA, Kožich V, Santra S, et al. Guidelines for the diagnosis and management of cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2017b;40(1):49-74.
- Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24(1):67-74.
- Tan X, Patel I, Chang J. *Review of the Four Item Morisky Medication Adherence Scale (MMAS-4) and Eight Item Morisky Medication Adherence Scale (MMAS-8)*. University of Minnesota, College of Pharmacy; 2014 Retrieved from the University of Minnesota Digital Conservancy, <http://hdl.handle.net/11299/171823>.
- Al-Dewik NI, Morsi HM, Samara MM, et al. Is adherence to Imatinib Mesylate treatment among patients with chronic myeloid leukemia associated with better clinical outcomes in Qatar? *Clin Med Insights Oncol*. 2016;10:CMO.S32822.
- Södergård B, Halvarsson M, Lindbäck S, Sönnernborg A, Tully MP, Lindblad ÅK. Differences in adherence and motivation to HIV therapy—two independent assessments in 1998 and 2002. *Pharm World Sci*. 2006;28(4):248-256.
- Gramer G, Abdoh G, Ben-Omran T, et al. Newborn screening for remethylation disorders and vitamin B12 deficiency-evaluation of new strategies in cohorts from Qatar and Germany. *World J Pediatr*. 2017;13(2):136-143.
- Yap S, Naughten E. Homocystinuria due to cystathionine beta-synthase deficiency in Ireland: 25 years' experience of a newborn screened and treated population with reference to clinical outcome and biochemical control. *J Inherit Metab Dis*. 1998;21(7):738-747.
- Yap S, Rushe H, Howard PM, Naughten ER. The intellectual abilities of early-treated individuals with pyridoxine-nonresponsive homocystinuria due to cystathionine beta-synthase deficiency. *J Inherit Metab Dis*. 2001;24(4):437-447.
- El Bashir H, Dekair L, Mahmoud Y, Ben-Omran T. Neurodevelopmental and cognitive outcomes of classical Homocystinuria: experience from Qatar. *JIMD Rep*. 2015;21:89-95.
- Gröbe H. Homocystinuria (cystathionine synthase deficiency). Results of treatment in late-diagnosed patients. *Eur J Pediatr*. 1980;135(2):199-203.
- Adam S, Almeida MF, Carbasius Weber E, et al. Dietary practices in pyridoxine non-responsive homocystinuria: a European survey. *Mol Genet Metab*. 2013;110(4):454-459.
- Schiff M, Blom HJ. Treatment of inherited homocystinurias. *Neuropediatrics*. 2012;43(6):295-304.
- Walter JH, Wraith JE, White FJ, Bridge C, Till J. Strategies for the treatment of cystathionine beta-synthase deficiency: the experience of the Willink biochemical genetics unit over the past 30 years. *Eur J Pediatr*. 1998;157(Suppl 2):S71-S76.

24. Garland J, Prasad A, Vardy C, Prasad C. Homocystinuria: challenges in diagnosis and management. *Paediatr Child Health*. 1999;4(8):557-562.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Al-Dewik N, Ali A, Mahmoud Y, et al. Natural history, with clinical, biochemical, and molecular characterization of classical homocystinuria in the Qatari population. *J Inherit Metab Dis*. 2019;42:818–830. <https://doi.org/10.1002/jimd.12099>